

(19)



Europäisches Patentamt  
European Patent Office  
Office européen des brevets

(11) Publication number:

0 341 551  
A1

f7

(12)

# EUROPEAN PATENT APPLICATION

(21) Application number: 89107912.1

(22) Date of filing: 02.05.89

(51) Int. Cl.<sup>4</sup>: C07C 63/66 , C07C 65/28 ,  
C07C 69/94 , C07F 9/28 ,  
C07C 51/00 , C07C 67/00 ,  
C07C 149/273 , A61K 31/19 ,  
A61K 31/235

(30) Priority: 13.05.88 GB 8811423

(43) Date of publication of application:  
15.11.89 Bulletin 89/46

(54) Designated Contracting States:  
AT BE CH DE ES FR GB GR IT LI NL SE

(71) Applicant: BAYER AG

D-5090 Leverkusen 1 Bayerwerk(DE)

(72) Inventor: Rosentreter, Ulrich, Dr.  
Kondorweg 23

D-5600 Wuppertal 1(DE)

Inventor: Kluender, Harold, Dr.

65 Ocean Ave

West Haven, CT 06516(US)

Inventor: Abram, Trevor S., Dr.

214 Marlow Bottom

Marlow Bucks(US)

Inventor: Norman, Peter, Dr.

4 St. Andrews Way Cippenham

Slough Berks, SL1 5NX(GB)

Inventor: Tudhope, Stephen R., Dr.

47 Kentons Lane

Windsor Berks, SL4 4JH(GB)

(54) Alkenoic acid derivatives.

(57) New alkenoic acid derivatives can be prepared by reaction of corresponding aldehydic esters with phosphorous compounds in inert solvents and in the presence of bases followed by hydrolysis of the intermediate esters. The new alkenoic acid derivatives can be used as active compounds in medicaments.

EP 0 341 551 A1

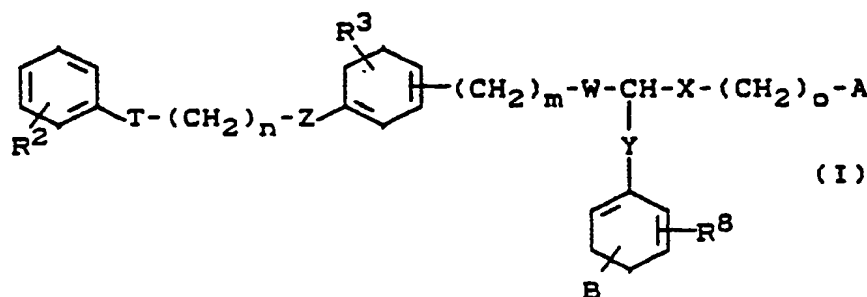
-NaCl 137, MgCl<sub>2</sub> 2.1, KCl 2.7, NaH<sub>2</sub>DO<sub>4</sub> 0.5, CaCl<sub>2</sub> 2.4, NaHCO<sub>3</sub> 11.9, D-glucose 9.2.

## Results

Contractions were normalised to the histamine-induced maximum for each preparation. The responses to analogue, LTD<sub>4</sub> and LTD<sub>4</sub> plus analogue were then expressed as a percentage of the maximum LTD<sub>4</sub> response in the appropriate control preparation. EC<sub>50</sub> (that concentration required to induce a 50% maximal LTD<sub>4</sub> response) values for 'test' and control tissues were calculated using a least squares linear regression program. These values were used to calculate a pK<sub>B</sub> to qualify the degree of antagonism where appropriate.

## Claims

1. Alkenoic acid derivatives of the general formula



in which

X and Y are identical or different and represent sulfur, sulfoxide, sulfone, an alkylene chain, -SCH<sub>2</sub>-, or oxygen or a direct bond,

W represents -CH=CH- or -CH<sub>2</sub>-CH<sub>2</sub>-

o represents a number 1 to 5

A and B are identical or different and represent carboxyl, carboxymethylene, tetrazolyl or tetrazolyl-methylene, or -CO<sub>2</sub>R<sup>9</sup> or -CH<sub>2</sub>CO<sub>2</sub>R<sup>9</sup> or -CONR<sup>10</sup>R<sup>11</sup> or nitrile

n represents a number 1 to 10,

m represents a number 0 to 7,

T and Z are identical or different and represent oxygen or a direct bond and

R<sup>2</sup>, R<sup>3</sup>, R<sup>8</sup> are identical or different and represent hydrogen, alkyl, alkoxy, halogen, trifluoromethyl, trifluoromethoxy, cyano or nitro

R<sup>9</sup> is lower alkyl and R<sup>10</sup> and R<sup>11</sup> are hydrogen, lower alkyl, alkylsulfonyl or arylsulfonyl or together are an alkylene chain to form a ring and their salts have been prepared.

2. Alkenoic acid derivatives according to claim 1, wherein

X and Y are identical or different and represent sulfur, sulfoxide, sulfone, a methylene group, -SCH<sub>2</sub>-, oxygen, an ethylene group or a direct bond,

W represents -CH=CH- or -CH<sub>2</sub>CH<sub>2</sub>-

o represents a number 1 to 4,

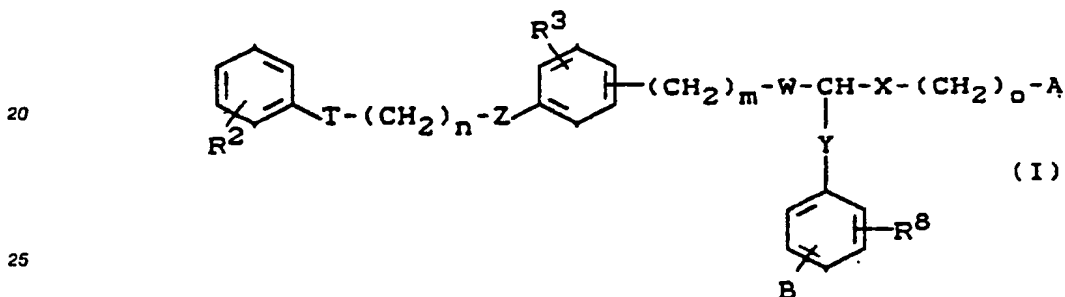
n represents a number 1 to 7,

m represents a number 0 to 5,

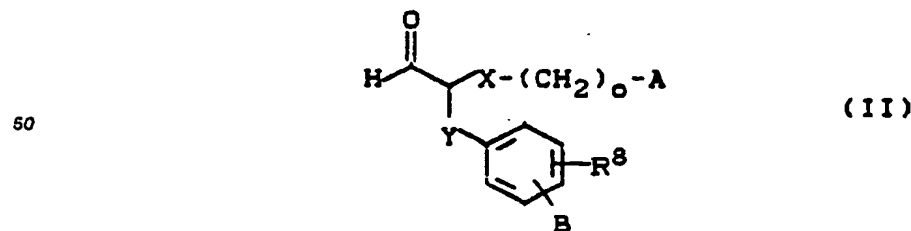
T and Z are identical or different represent oxygen or a direct bond and

R<sup>2</sup>, R<sup>3</sup>, R<sup>8</sup> are identical or different and represent hydrogen, lower alkyl, lower alkoxy, fluorine, chlorine or trifluoromethyl and their salts.

3. Alkenoic acid derivatives according to claims 1 and 2, where in  
 X represents sulfur, sulfoxide or a methylene group,  
 Y represents sulfur, a methylene group,  $-\text{SCH}_2-$  or a direct bond,  
 W represents  $-\text{CH}=\text{CH}-$ ,  
 5  $\text{R}^2$  and  $\text{R}^3$  represent H,  
 $\text{R}^2$  represents H or F,  
 o represents a number 1, 2, 3 or 4,  
 n represents a number 2, 3, 4, 5 or 6,  
 m represents a number 0, 1 or 2,  
 10 T represents oxygen or a direct bond  
 Z represents oxygen or a direct bond  
 A represents carboxyl or ester thereof,  
 B represents para carboxyl or ester thereof, and their salts.  
 4. Alkenoic acid derivatives according to claims 1 to 3 for therapeutic treatment.  
 15 5. Process for the preparation of alkenoic acid derivatives of the formula



- in which  
 30 X and Y are identical or different and represent sulfur, sulfoxide, sulfone, an alkylene chain,  $-\text{SCH}_2-$ , oxygen or a direct bond,  
 W represents  $-\text{CH}=\text{CH}-$  or  $-\text{CH}_2-\text{CH}_2-$ ,  
 o represents a number 1 to 5  
 A and B are identical or different and represent carboxyl, carboxymethylene, tetrazolyl or tetrazolyl-  
 35 methylene, or  $-\text{CO}_2\text{R}^9$  or  $-\text{CH}_2\text{CO}_2\text{R}^9$  or  $-\text{CONR}^{10}\text{R}^{11}$  or nitrile wherein  $\text{R}^9$  is lower alkyl and  
 $\text{R}^{10}$  and  $\text{R}^{11}$  are hydrogen, lower alkyl, alkylsulfonyl or arylsulfonyl or together are an alkylene chain to form  
 a ring,  
 n represents a number 1 to 10,  
 m represents a number 0 to 7,  
 40 T and Z are identical or different and represent oxygen or a direct bond  
 and  
 $\text{R}^2$ ,  $\text{R}^3$ ,  $\text{R}^8$  are identical or different and represent hydrogen, alkyl, alkoxy, halogen, trifluoromethyl,  
 trifluoromethoxy, cyano or nitro  
 and their salts, characterized in that  
 45 aldehydes of the general formula (II)



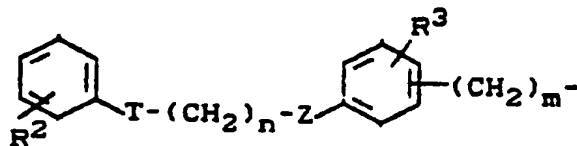
- in which  
 X, Y, o and  $\text{R}^8$  have the above mentioned meaning and  
 A and B are identical or different and represent  $\text{CO}_2\text{R}^9$  or  $\text{CH}_2\text{CO}_2\text{R}^9$  or  $\text{CONR}^{10}\text{R}^{11}$  or nitrile where in  $\text{R}^9$

represents lower alkyl and  $R^{10}$  and  $R^{11}$  represent lower alkyl, a methylene chain or H,  
are reacted with phosphorus compounds of the general formula (III)

$R^1-CH_2-U$  (III)

in which

$R^1$  is

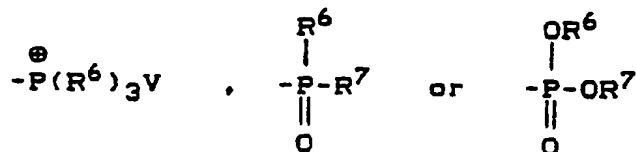


in which

$R^2$ , T, n, Z,  $R^3$  and m have the above mentioned meaning

and

U represents a group of the formula



where

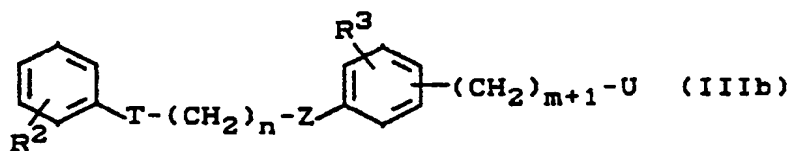
$R^6$  and  $R^7$  are identical or different and denote alkyl or phenyl

and

V denotes a halide anion or a tosylate anion in inert solvents in the presence of bases, whereby the esters  
are then hydrolysed or partially hydrolysed.

6. Process according to claim 5, characterised in that it is carried out in the temperature range from  
 $-80^\circ\text{C}$  to  $+70^\circ\text{C}$ .

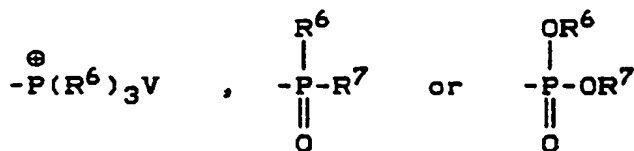
7. Phosphorous compounds of the formula



wherein

$R^2$  and  $R^3$  are identical or different and represent hydrogen, alkyl, alkoxy, halogen, trifluoromethyl,  
trifluoromethyl, cyano or nitro,

U represents a group of the formula



where

$R^6$  and  $R^7$  are identical or different and denote alkyl or phenyl

and

V denotes a halide anion or tosylate anion.

T and Z are identical or different and represent oxygen or a direct bond,  
m represents a number 0 to 7 and  
n represents a number 1 to 10.

8. Medicaments containing alkenoic acid derivatives according to claims 1 to 3.

5 9. Medicaments according to claim 8, characterised in that it contains about 0.5 to 98% by weight of the alkenoic acid derivatives.

10. Use of alkenoic acid derivatives according to claims 1 to 3 for the preparation of medicaments.

11. Use according to claims 9 and 10, for the preparation of medicaments for the treatment of diseases of the circulatory system and of the respiratory system.

10

15

20

25

30

35

40

45

50

55



EP 89107912.1

DOCUMENTS CONSIDERED TO BE RELEVANT				
Category	Citation of document with indication, where appropriate, of relevant passages	Relevant to claim	CLASSIFICATION OF THE APPLICATION (Int. Cl. 4)	
D, A	<u>GB - A - 2 184 121</u> (LILLY) * Claims; abstract; pages 4, 5 * --	1, 5, 7, 8-11	C 07 C	63/66
			C 07 C	65/28
			C 07 C	69/94
			C 07 F	9/28
			C 07 C	51/00
A	<u>EP - A2 - 0 084 667</u> (BASF) * Claims; page 9 * ----	1, 5, 7, 8-10	C 07 C	67/00
			C 07 C	149/273
			A 61 K	31/19
			A 61 K	31/235
			TECHNICAL FIELDS SEARCHED (Int. Cl. 4)	
			C 07 C	63/00
			C 07 C	65/00
			C 07 C	69/00
			C 07 C	149/00
The present search report has been drawn up for all claims				
Place of search VIENNA		Date of completion of the search 09-08-1989	Examiner HOFBAUER	
CATEGORY OF CITED DOCUMENTS				
X : particularly relevant if taken alone		T : theory or principle underlying the invention		
Y : particularly relevant if combined with another document of the same category		E : earlier patent document, but published on, or after the filing date		
A : technological background		D : document cited in the application		
O : non-written disclosure		L : document cited for other reasons		
P : intermediate document		& : member of the same patent family, corresponding document		